

Cutaneous Findings in Patients with Acromegaly

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SUMMARY Acromegaly is a systemic syndrome caused by overproduction of growth hormone. The syndrome affects cutaneous, endocrine, cardiovascular, skeletal, and respiratory systems. Cutaneous manifestations of acromegaly are various, usually being the first presenting findings of the disease. Forty-nine patients with acromegaly, followed-up at a tertiary referral hospital, underwent dermatological examination. There were 27 (55.1%) female and 22 (44.9%) male patients. The age at onset of the disease was older in females than males ($P=0.045$). Most patients had acral enlargements, large triangular nose, coarse face, thickened lower lip, and prognathism. Fourteen (28.6%) patients had multiple cherry angiomas, five (10.2%) had varicose veins in lower limbs, and two (4.1%) had psoriasis. In conclusion, a wide spectrum of cutaneous symptoms and features may be associated with acromegaly. Detailed dermatological examination of patients with acromegaly should be an essential component of systemic evaluation. Future prospective studies investigating the relationships between changes in skin signs, hormone levels, and response to treatments may help understand details of skin involvement in acromegaly.

KEY WORDS: acromegaly, cutaneous manifestations, multiple cherry angiomas, psoriasis, varicose veins

INTRODUCTION

Acromegaly is a systemic syndrome caused by overproduction of growth hormone (GH) in adulthood, after or around the time that the epiphyses close (1,2). The annual incidence of acromegaly is about 3-4 cases *per* million, with an estimated prevalence of 40 to 70 cases *per* million (3). The underlying pathology is pituitary adenoma in about 95% of patients. The diagnosis of acromegaly depends on the detection of high GH levels after oral glucose tolerance test (OGTT). After hormonal diagnosis, magnetic resonance imaging of the brain reveals the presence and size of adenoma and invasion to the adjacent tissues. Acromegaly affects both genders equally (4) and occurs most frequently in middle age. The mean age of diagnosis is 40 years in males and 45 years in

females (5). The syndrome affects almost every organ system, mainly cutaneous, endocrine, cardiovascular, skeletal, and respiratory systems, due to increased levels of GH and insulin-like growth factor 1 (IGF1). High levels of GH and IGF1 are associated with high morbidity and mortality rates (6). Thus, early diagnosis is very important to initiate aggressive appropriate treatments to lower these hormones. However, diagnosis of the disease is usually made with a delay of 7-10 years after the onset of symptoms (4,7).

Cutaneous changes in acromegaly are classical features of the disorder, being an important clue for early diagnosis (2,8). Increased production of GH and IGF1 induces morphological alterations in skin morphology. Oversecretion of IGF1 is stimulated by GH

and acts as the primary mediator of growth promoting effects of GH (5). After binding to IGF1 receptors (IGFRs), proliferation and/or over-function of many cell lines such as keratinocytes, fibroblasts, pilar unit, Schwann cells, muscle cells, or medial and endothelial cells of arteries are stimulated (2,8-11). Therefore, acromegaly presents with various cutaneous and systemic manifestations. Skin thickening and edema occur due to increased proliferation of keratinocytes and fibroblasts, accumulation and infiltration of glycosaminoglycan deposits (12). Besides these, periosteal new bone and cartilage formation causes increase in skeletal growth (13). Typical earliest and obvious manifestations involve skin and soft tissue, especially the face (marked facial lines, eyelid edema, large pores, widened and thickened nose, thick lips, prognathism, teeth separation, etc.) and extremities (hand and foot enlargement, heel pads, hard and thick nails) (5).

Acromegaly may present with various cutaneous changes. Therefore, suspicion and careful evaluation of the skin findings of the disorder are very important (8). In this paper, dermatological symptoms and features of patients with acromegaly who were followed-up at a tertiary hospital are described and discussed through previously published reports.

PATIENTS AND METHODS

This was a cross-sectional study conducted prospectively between February and August 2011 at a single tertiary referral hospital. A total of 49 patients who were on treatments in the outpatient endocrinology clinic were enrolled in the study. Of the patients, 33 were diagnosed in our endocrinology clinic and 16 were referred from other health centers for their maintenance therapies. All patients were diagnosed based on appropriate criteria for acromegaly and all had pituitary adenoma. Clinical findings along with (i) high IGF1 levels according to sex and age; (ii) random GH level $>0.4\mu\text{g/L}$; and (iii) no GH suppression ($>1\mu\text{g/L}$) after OGTT indicated the diagnosis of acromegaly (4,14).

The symptoms and findings of dermatological and systemic examinations at the time of diagnosis were reviewed from the patient charts. Complete dermatological examination was performed for each patient at study entry. The estimated onset of acromegaly was calculated from age at presentation in years and duration of symptoms in years. The study was approved by the local ethics committee and conducted according to the Declaration of Helsinki. All participants gave their written informed consent.

Statistical analyses

Evaluation of normality was performed with the Kolmogorov-Smirnov test. Normally distributed continuous variables were expressed as mean and standard deviation (mean \pm SD), and were compared with Student's *t*-test. Non-normally distributed continuous variables were expressed as median. $P<0.05$ was accepted to be statistically significant. All statistical analyses were performed using the SPSS version 17.0 statistical software package (SPSS Inc., Chicago, Illinois, USA).

RESULTS

The study included 27 (55.1%) female and 22 (44.9%) male patients, mean age 45.5 ± 11.6 years (female: 49.4 ± 10.4 , male: 40.7 ± 11.4) at study entry. The acromegaly symptoms were present for 8.7 ± 5.6 years (range: 2 months-30 years). The mean estimated onset of acromegaly was 39.9 ± 12.5 years for females and 33.1 ± 10.1 years for males. The age at onset was older in females than males ($P=0.045$). Duration of the disease was similar between female and male patients ($P=0.281$). Common presenting complaints in the patients were acral enlargements (71.4%), headache (40.8%), coarse face (22.4%), and hoarseness (10.2%). Besides, some patients were diagnosed during evaluation for dysglycemia, amenorrhea, and thyroid disorders (Table 1).

Dermatological findings of the patients are listed in Table 2. Most of the patients had acral enlargements, large triangular nose, coarse face, thickened lower lip, and prognathism on dermatological exami-

Table 1. Presenting complaints of patients with acromegaly

Presenting complaints	n	%
Acral enlargements	35	71.4
Headache	20	40.8
Coarse face	11	22.4
Hoarseness	5	10.2
Hyperhidrosis	3	6.1
Hirsutism	3	6.1
Dysglycemia	3	6.1
Vision defects	3	6.1
Neurologic problem	2	4.1
Carpal tunnel syndrome	2	4.1
Amenorrhea	2	4.1
Thyroid disorder	2	4.1
Sleep apnea	2	4.1
Arthralgia	2	4.1
Galactorrhea	1	2.1

nation. Cutis verticis gyrata was observed in 9 male and 3 female patients. Seborrheic keratoses (SK) were detected in 9 (18.4%) patients, age range 43-66 years. Hirsutism accompanied acromegaly in 4 female patients. All of them also had amenorrhea. Hypertrichosis over the non-androgen dependent areas of the body was seen in 8 male and 3 female patients. Five (10.2%) patients had varicose veins in lower limbs. Two patients had biopsy proven psoriasis, which emerged before acromegaly symptoms and partially regressed after the initiation of treatment for acromegaly.

Of the study patients, 17 (34.5%) had hypertension, 11 (22.4%) diabetes mellitus, 6 (12.4%) impaired glucose tolerance, 23 (46.9%) thyroid disease including multinodular goiter ($n=17$; 34.7%), hypothyroidism ($n=4$; 8.2%), thyroiditis ($n=2$; 4.1%), and two (4.1%) had panhypopituitarism. Hypertension, diabetes mellitus, and thyroid disorders were more frequent in females than males (P values, 0.028, 0.043, and 0.002, respectively).

Surgical operations were performed in 48 patients. One patient could not undergo surgical treatment because of associated co-morbidities. Six patients underwent conventional radiotherapy postoperatively. Medical therapy with somatostatin analogs was administered to 45 patients.

DISCUSSION

This study was conducted to analyze dermatological features in a group of patients with acromegaly. We documented that the patients with acromegaly demonstrated various cutaneous signs although they were on therapies. In our study group, acral and facial changes were the most common presenting symptoms at admission and they were also the most common findings on our dermatological examinations. These features were more frequent than in the series of 256 cases reported by Nabbaro (2). On the other hand, Arya *et al.* report on a recent study in 34 patients with facial and acral involvement in all of them (15).

Acrochordons in acromegalic patients have been reported in a wide range of 5.9% to 45% of cases (15-17). In the general population, acrochordons are usually associated with diabetes mellitus, insulin resistance, and dyslipidemia (18). Hyperinsulinemia elevates free IGF-1 levels and stimulation of IGF1Rs induces epidermal hyperplasia (19). Although acrochordons seem to be a component of metabolic complications of acromegaly, the association with colonic polyps still suggests a possible connection with acromegaly itself (18). Acanthosis nigricans is another cutaneous manifestation, which is not spe-

Table 2. Cutaneous findings detected in patients with acromegaly

Cutaneous findings	n	%
Acral enlargements	43	87.8
Course face	43	87.8
Large triangular nose	40	81.6
Thickened lower lip	38	77.6
Prognathism	39	79.4
Macroglossia	33	67.3
Acrochordons	34	69.4
Widened skin pores	33	67.3
Hyperhidrosis	25	51.0
Eyelid edema	24	49.0
Thickened heel pads	23	46.9
Oily skin	17	34.7
Thickened nails	14	28.6
Cherry angiomas	14	28.6
Cutis verticis gyrata	12	24.5
Hypertrichosis	11	22.4
Seborrheic keratoses	9	18.4
Acne	7	14.3
Acanthosis nigricans	7	14.3
Clubbing	5	10.2
Varicose veins	5	10.2
Hirsutism	4	8.2
Psoriasis	2	4.1

cific for acromegaly since it may accompany various metabolic and hormonal disturbances. In our study, the frequency of acanthosis nigricans was comparable to previous large series (15,17).

Detection of IGF1 immunoreactivity in the outer root sheath, hair matrix cells, sebaceous gland, eccrine sweat glands, and myoepithelial cells of the secretory portion of eccrine sweat glands (20) suggests that hypertrichosis, oily skin, and hyperhidrosis are induced by high IGF1 levels in acromegaly. Hyperhidrosis is a common complaint of acromegalic patients with a frequency ranging between 50% and 88% (2,21). It was observed almost in half of our patients. Since histology of the eccrine sweat glands in patients with acromegaly is similar with healthy controls, hyperhidrosis seems to be related to hyperfunction of eccrine sweat glands rather than increased gland number (18). IGF1 was found to affect the



Figure 1. Typical cutaneous manifestations of acromegaly in different patients: coarse face, large triangular nose, and thickened lower lip (a); eyelid edema and prognathism (b); thickened heel pads (c); acral enlargement of hands (d).

human hair cycle by stimulating the growth of hair follicles potently and preventing them to enter the catagen phase (11). Although IGF/IGFR interaction seemed to be the main regulator of the pathogenesis of hirsutism and hypertrichosis of the patients, the interaction of IGF axis and androgens has not been investigated in detail. A small number of female acromegalic patients with hirsutism had normal levels of testosterone in the series of Nabarro (2). On the other hand, high IGF1 levels were found to be associated with adrenal hyperandrogenism in hirsute women without acromegaly (22). The authors suggested the role of IGF axis in the development of hirsutism. Detailed studies with a large number of acromegalic patients with hirsutism and hypertrichosis are needed to establish the association of high IGF1 levels and levels of androgens.

Cutis verticis gyrata was one of the least frequent skin signs reported in the case series of acromegaly. It was not seen in the series of Arya *et al.* (15), and only 1.6% in the study by Nabarro (2). In contrast, in our study, it was more frequently observed (24.5%) and was found to be more common in male acromegalic patients. Because of its subtle appearance under hairs, which prevents the lesion from being noticed by the patient or physician until it becomes obvious, the actual frequency of cutis verticis gyrata may be higher than reported.

Beside typical cutaneous manifestations, multiple cherry angiomas (28.9%) and varicose veins (10.2%)

were observed in our study group. These findings were not mentioned in previous series. Cherry angiomas are overgrowths of endothelial cells, categorized in vascular tumors. They are suggested to be a result of cutaneous angiogenesis with abnormal proliferation (23). The etiology and true prevalence of cherry angiomas are not well-known. Since 75% of adults were shown to have cherry angiomas, aging process has been suggested to have a role in the pathogenesis (24). In our study, most of the patients with cherry angiomas were aged above 50. This may support the effect of aging; however, recent findings about the role of IGF1 in angiogenesis indicated the role of hormonal disturbances in acromegaly (25-27). The IGF1/IGF1R signaling pathway may induce cutaneous angiogenesis leading to the development of multiple cherry angiomas in patients with acromegaly.

Varicose veins are a common venous disease of lower limbs in the general population. Reflux of blood in deep venous system due to incompetent valves and vein wall dilation are at the center of the pathophysiology of varicose vein formation. Matrix metalloproteinase (MMP) activation and fibrosis lead to vein wall damage (28). Varicose veins and relationship with acromegaly have not been mentioned before. Since increased MMP levels have recently been demonstrated in acromegalic patients (29), vein wall damage due to MMP activation may be a trigger in varicose vein formation.

Seborrheic keratosis is one of the most common skin tumors. The role of IGF in SK is not clear. Hodack *et al.* investigated IGFRs in 10 specimens of long standing and clinically non-enlarging SKs and failed to show overexpression of IGFRs in suprabasal layers (20). Stein *et al.* report on a patient with florid eruption of SK associated with malignant tumor and high levels of IGF (30). The size and number of SK were decreased as IGF levels normalized. To date, SK has not



Figure 2. Psoriasis plaques around the ankle of a patient with acromegaly.

been noted in the cutaneous findings of acromegaly. Since it is frequent in general population, to mention this finding as a manifestation of the syndrome and to establish a true association with IGF levels in patients with acromegaly requires comparison studies with healthy individuals.

IGF1 is one of the growth factors involved in the pathogenesis of psoriasis (31). It induces cell division, proliferation of epidermal keratinocytes, and epidermal hyperplasia (32). Recently, El-Komy *et al.* demonstrated a significant increase in IGF1 mRNA in psoriatic plaques and reduction of its lesional levels after treatment with methotrexate and psoralen plus ultraviolet A light therapies (33). Acromegalic patients with psoriasis have been reported to benefit from pituitary tumor excision (34) or therapy with somatostatin analogs (35). In our series, two patients had psoriasis, which developed before the symptoms of acromegaly. The lesions regressed but not totally improved after the treatment for acromegaly.

In our study, the present cutaneous manifestations of the patients were objectively defined. The major limitation of the present study was the unavailability to document the changes in cutaneous manifestations after the treatment periods and during their follow-up because of its cross-sectional nature. In previous studies, it has been reported that several cutaneous manifestations of acromegaly might become stable or regress after successful inhibition of GH and IGF1 oversecretion (2,5). However, relationship between the change in cutaneous manifestations and response to therapies has not been fully investigated. Future prospective studies investigating the relationship between changes in skin signs, hormone levels, and response to treatments may help understand details of the skin involvement in acromegaly.

CONCLUSION

We described cutaneous features of acromegaly in detail as well as some other findings that have not been reported before in acromegalic patients in the present study. Dermatological examination of patients with acromegaly is important as well as their systemic evaluation. Collaboration of dermatologists on acromegaly patient examination at their first admission and at regular visits is necessary for appropriate and complete evaluation of these patients.

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